

# National Guideline on the Management of the Viral Hepatitides A, B & C

## Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases)

### Hepatitis A virus infection

#### Aetiology

Caused by a picorna (RNA) virus. It is particularly common in areas of the world where sanitation is poor (developing countries) and largely affects children there. In the developed world it is less common (1325 cases reported in England and Wales, 1999) and causes disease in all age groups [1].

#### Transmission:

- Faeco-oral (via food, water, close personal contact) [2-7].
- Outbreaks have been reported in gay men, linked to oro-anal or digital-rectal contact, multiple sexual partners, anonymous partners, sex in public places and group sex [8-14]. However, several seroprevalence studies in the UK, Spain, USA and Italy show a similar rate of hepatitis A (IgG) antibodies in homosexual and heterosexual men [12,15,16].
- Outbreaks have also been reported amongst intravenous drug users [17-19], in institutions for learning difficulties, and in contaminated batches of factor VIII [20-22].
- Patients are infectious for approximately two weeks before and one week after the jaundice by the non-parenteral routes but virus can be found in the blood and stool until after the serum amino-transferase levels have peaked [23].

#### Clinical Features

Incubation Period: 15-45 days [2,3,24]

#### Symptoms [24]

Most children and up to half of adults are asymptomatic or have mild non-specific symptoms with little or no jaundice.

In the more 'typical' case there are two phases of symptoms -

- *The prodromal illness:* flu-like symptoms (malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts for 3-10 days. This is followed by -
- *The icteric illness:* jaundice (mixed hepatic and cholestatic) associated with anorexia, nausea and fatigue which usually lasts for 1-3 weeks. It can persist for 12 or more weeks in a minority of patients who have cholestatic symptoms (itching and deep jaundice) [25]. Fever is not found in this phase.

#### Signs [16]

- None specific in the prodromal phase.
- Icteric phase - jaundice with pale stools and dark urine. Liver enlargement/tenderness and signs of dehydration are also common.

#### Complications

- Fulminant hepatitis complicates approximately 0.4% of cases, although 15% of patients may require hospital care, of whom a quarter will have severe hepatitis (P.T.> 3 seconds prolonged or bilirubin >170µmoles/l) [26,27]. Fulminant hepatitis A (up to 40%) is particularly common in patients already infected with chronic hepatitis C [28].
- Chronic infection (>6 months) has only been reported in a tiny number of case-reports [29].

- The overall mortality is approximately 0.2% [26,27].
- Pregnancy - The infection does not have any teratogenic effects but there is an increased rate of miscarriage and premature labour, proportional to the severity of the illness [30,31]. There have been two case reports of possible vertical transmission [32,33].

### Diagnosis

#### Serology

- Confirmed by a positive serum Hepatitis A virus - specific IgM (HAV-IgM) which remains positive for six months or more [34,35]. HAV-IgG does not distinguish between current or past infection and may remain positive for life [34,36].

#### Other tests

- Serum/plasma amino-transferases (AST/ALT) 500-10,000 i.u./l. Bilirubin up to 500  $\mu$ moles/l. Alkaline phosphatase levels < 2x the upper limit of normal, but higher if there is cholestasis [24,26-28].
- Prothrombin time (PT) prolongation by more than 5 seconds suggests developing hepatic decompensation [24,26].

### Management

#### General Advice

- Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (III,B) [2-4,7,37]
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Hepatitis A is a notifiable disease.

#### Further Investigations

Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate.

#### Acute icteric hepatitis

- Mild/moderate (80%) - manage as an outpatient emphasising rest and oral hydration (III, B) [24].
- Severe attack with vomiting, dehydration or signs of hepatic decompensation (change in conscious level or personality) - admit to hospital (III, B) [26,27].

#### Pregnancy and Breast Feeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens [31].
- Breast feeding can be continued but consider giving Human Normal Immunoglobulin (HNIG) 125mg.i.m. to the baby, although most children will have mild or asymptomatic infection (IV,C) [38].

#### Sexual and Other Contacts

- Partner notification should be performed for at-risk homosexual contacts (oro/anal, digital/rectal and penetrative anal sex) within the period two weeks before to one week after the onset of jaundice. This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination ) to be contacted via the public health authorities (consultant in communicable control (CCDC) or equivalent). The CCDC has a duty of confidentiality to the index patient.
- HNIG 250-500 mg. intramuscularly should be considered for close household and sexual contacts who are not known to be immune (but see below) (Ib, A) [38,39].
- HNIG works best if given in the first few days after first contact with an efficacy of 90% and is unlikely to give any protection more than two weeks after first exposure. Remember, patients are most infectious for two weeks before the jaundice (i.e. before the illness is recognised).
- Hepatitis A vaccine may also be given after exposure (IIa, B) [38, 40,41].

- Hepatitis A vaccine schedule: doses at 0 and 6-12 months, 95% protection for at least five years (Ib, A)[42-45]. Current advice is to revaccinate after ten years (IIb, B) [42-8]. HIV-positive patients respond (antibody production) in 73-88% but titres are lower than in HIV-negative individuals (IIa, B)[46,47]. There is a combined Hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (IIa, B) [48,49].
- If an outbreak is suspected or if the index case is a food handler, notify the local CCDC/public health department by telephone (IV, C)[38].

#### Follow-Up

- See at one or two weekly intervals until amino-transferase levels are normal (usually 4 -12 weeks) (IV, C).
- Immunity is usually lifelong. [34,36]

#### Primary Prevention

- Current evidence still suggests that most gay men are not at increased risk for hepatitis A infection [12,15,16] and therefore universal vaccination in this group cannot be firmly recommended (III, B). However, many outbreaks have been reported amongst gay men in large cities and therefore clinics in these areas (e.g. central London) should offer vaccination, particularly when increased rates of infection in gay men have been recognised locally (III, B) [8-14, 38].
- Evidence is accumulating that intravenous drug users and patients with chronic hepatitis C infection should also be vaccinated (III, B) [17-19, 28, 38].
- Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure and for people at risk in an outbreak (Ib, A) [38].
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (IV, C) [38].

## Hepatitis B virus infection

### Aetiology

Caused by an hepadna (DNA) virus. It is endemic world-wide, apart from isolated communities, with very high carriage rates (up to 20%) particularly in South and East Asia, but also in Southern Europe, Central and South America, Africa and Eastern Europe. In the UK carriage varies from 0.01-0.04% in blood donors to >1% in intravenous drug users and gay men.[51]. In 1999, 715 acute and 1579 total (acute/chronic/undetermined) cases were reported in England and Wales [1].

### Transmission

- Sexual transmission occurs in unvaccinated gay men and correlates with multiple partners, unprotected anal sex and also with oro-anal sex (“rimming”) [52-56]. Transmission also occurs after heterosexual contact e.g. 18% infection rates for regular partners of patients with acute hepatitis B [57-59]. Sex workers are also at higher risk [60,61].
- Other routes are: parenteral (blood, blood products, drug-users sharing needles and syringes, needle-stick, acupuncture) and vertical (infected mother to infant) [53, 58, 62-65].
- Sporadic infection occurs in people without apparent risk factors, in institutions for learning difficulties and also in children in countries of high endemicity, but in these cases the means of transmission is poorly understood [66,67].

### Clinical Features

Incubation period. 40-160 days

### Symptoms

- Virtually all infants and children have asymptomatic acute infection. Asymptomatic infection is also found in 10-50% of adults in the acute phase and is especially likely in those with HIV co-infection [24, 68-70].
- The prodromal and icteric phases are very similar to hepatitis A, but may be more severe and prolonged [24].

### Signs

- As for hepatitis A in the acute phase.
- If chronic infection occurs there are often no physical signs. After many years of infection, depending on the severity and duration, there may be signs of chronic liver disease including spider naevi, finger clubbing, jaundice and hepato-splenomegaly, and in severe cases thin skin, bruising, ascites, liver flap and encephalopathy [54, 70-73].

### Complications

- Fulminant hepatitis occurs in less than 1% of symptomatic cases but carries a worse prognosis than that caused by hepatitis A [26].
- Chronic infection (>6 months) occurs in 5-10% of symptomatic cases but the rate is higher in immuno-compromised patients with HIV infection, chronic renal failure or those receiving immuno-suppressive drugs [68, 70-73]. Immunosuppressive treatment can also reactivate hepatitis B [74]. A higher rate of chronic infection is also found in patients at institutions for learning disabilities [66]. Almost all (>90%) of infants born to infectious (HBeAg +ve) mothers will become chronic carriers unless immunised [62,64].
- Concurrent hepatitis C infection can lead to fulminant hepatitis, more aggressive chronic hepatitis and increased risk of liver cancer [75-77]. Concurrent HIV infection may increase the risk of progression to cirrhosis [78].
- Mortality is less than 1% for acute cases. Between ten and fifty percent of chronic carriers will develop cirrhosis leading to premature death in approximately 50% [54, 68]. Ten percent or more of cirrhotic patients will progress to liver cancer.[54, 68, 77].
- Pregnancy- increased rate of miscarriage/premature labour in acute infection [31]. Risk of vertical transmission (see above) [62,64]

### Diagnosis

**Table 1 Hepatitis B serology [34, 54, 69]**

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs
Acute (early)	+	+	+	+	+	-	-
Acute (resolving)	+	-	+	+	-	+/-	-
Chronic (high infectivity)	+	+/-	-	+	+	-	-
Chronic (low infectivity)	+	-	-	+	-	+/-	-
Resolved (immune)	-	-	-	+	-	+/-	+/-
Successful vaccination	-	-	-	-	-	-	+

### Other tests

- Acute infection - see hepatitis A
- Chronic infection - in most cases the only abnormality to be found will be mildly abnormal amino-transferase levels (usually <100 i.u./l) and in many the liver function tests (LFT) will be normal. Only in severe late stage liver disease does the LFT become grossly abnormal [54, 69-73].

## Management

### General Advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact until they have become non-infectious or their partners have been successfully vaccinated (see below) (III,B) [53,54,57 62,79].
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood (IV, C) [62].
- Hepatitis B is a notifiable disease

### Further Investigations

- Screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (IIb,B)[52, 60].
- Other tests such as liver biopsy (for assessment of chronic disease) should be performed by specialists in this field (IV,C) [54, 69-73].

### Acute icteric hepatitis

- As for hepatitis A.

### Treatment of Chronic Infection

- Patients should be considered for alpha interferon therapy, 5-20 M.U. thrice weekly for twelve to thirty two weeks (Ib, A)[70-72, 80, 81]. Additional promising treatments, alone or in combination with interferon, include lamivudine (Ib, A), famciclovir (IIb, B), adefovir (IIb, B), thymosin alpha (Ib,A) and ribavirin (IIb, B)[82-88]. Response to interferon is highest (forty to fifty percent) in patients with adult-acquired infection with inflammatory liver disease who are not immunocompromised (Ib, A)[70-72]. Interferon treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer[89,90].
- Lamivudine and famciclovir will suppress hepatitis B viral replication during therapy of immunocompromised patients, including those with HIV, and may delay liver damage (IIb, B)[91-93]. Cure is unusual in these patients, anti-viral resistance often develops after prolonged monotherapy and rebound hepatitis can occur if the agent is stopped or if resistance ensues (IIb) [91, 94].
- Specific therapy is otherwise not indicated unless de-compensated liver disease ensues (IV, C) [54].

### Pregnancy and Breastfeeding

- Vertical transmission (mother to infant) of infection occurs in ninety percent of pregnancies where the mother is hepatitis B e antigen positive and in about ten percent of surface antigen positive, e antigen negative mothers. Most (>90%) of infected infants become chronic carriers [64, 67, 95].
- Infants born to infectious mothers are vaccinated from birth, usually in combination with Hepatitis B specific Immunoglobulin 200 i.u. i.m. (Ia, A) [64, 95]. This reduces vertical transmission by ninety percent.
- Infected mothers should continue to breast feed as there is no additional risk of transmission (III, C)[96].

### Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (IV,C) [37, 97, 98]. The infectious period is from two weeks before the onset of jaundice until the patient becomes surface antigen negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (IV,C)[62]. For screening of other non-sexual partners who may be at risk, discuss with the CCDC or equivalent.

- Specific hepatitis B immunoglobulin 500 i.u. intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needle-stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than seven days (Ib, A) [62, 99].
- An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7 and 21 days or 0, 1, 2 months with a booster at 12 months in either course) (Ib, A) [62, 63, 97, 98, 100, 101, 101A]..
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10i.u./l.) (Ib, A) [62, 97, 98, 101]

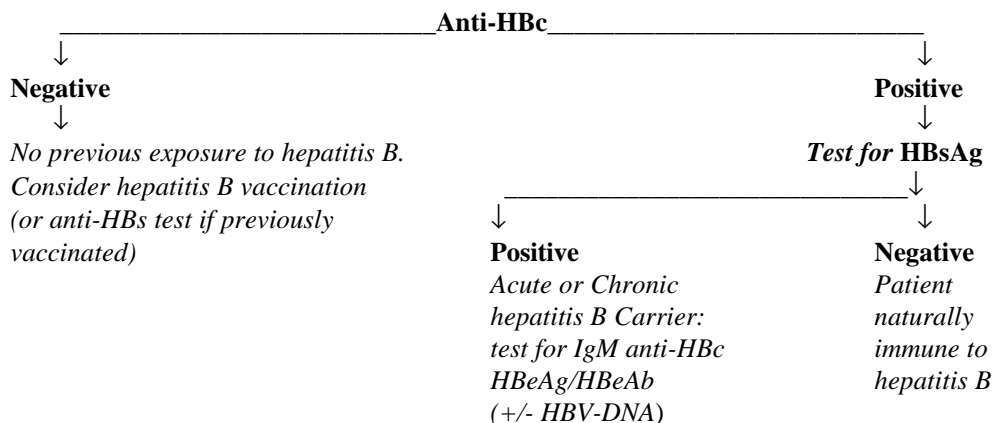
#### Follow-up.

- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after six months even if the LFT is normal [54, 68, 69].
- Chronic infection: If untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease (IV, C) [54, 68].
- Immunity after recovery from infection (surface antigen negative) is lifelong in over 90%.

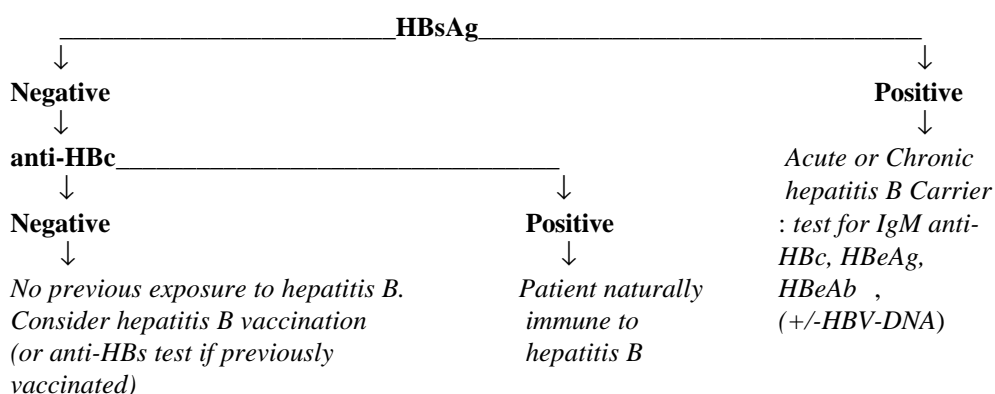
#### Screening and Primary Prevention

- Hepatitis B testing in asymptomatic patients should be considered in gay men, sex workers (of either sex), intravenous drug users, HIV-positive patients, sexual assault victims, people from countries where hepatitis B is common (outside of Western Europe, north America and Australasia), needle-stick victims and sexual partners of positive or high-risk patients (IV, C) [61, 62, 79,97,98]. If non-immune, consider vaccination (see below) (Ib, A) [62, 63, 100. 101]. If found to be chronic carriers consider referral for therapy (Ia, A) [70-73, 79-90].
- The simplest initial screening test in someone who is unvaccinated or is of unknown infection status is anti-HBc, with the addition of other tests as necessary (III,B)[102, 103]. Some units also screen for HBsAg initially (IV, C)[79, 97, 98]. Measure anti-HBs in those who have been vaccinated.

#### *Flow chart for hepatitis B screening using serum anti-HBc*



*Flow chart for hepatitis B screening using serum HBsAg*



- Vaccination should be offered to non-immune patients in most of the above groups (Ib, A) [62, 63, 100, 101, 101A]. The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (IV, C)[79, 97, 98]. HIV positive patients show a reduced response rate to the vaccine (approximately 40%) and become anti-HBs negative more quickly (IIb, B)[104-106].
- The vaccination schedule for both the monovalent and the combined hepatitis A+B vaccines is outlined in Table 2. The new ultra-rapid 0, 7, 21 day regimen offers the advantage of a potentially higher uptake of the full course. Test for response (anti-HBs >10i.u./l, ideally >100i.u./l) 4 - 12 weeks after the last dose (Ib, A)[62, 63, 100, 101]. Non- or poor responders usually respond to further doses (up to three injections), ideally as a repeat course (Ib, A) with response rates up to 100% (Ib, A)[107, 108]. New pre-S-containing vaccines are effective (Ib, A) and may also be used for conventional-vaccine non-responders (IIa, B) [109-113].

**Table 2 Vaccination Schedules for Hepatitis B using monovalent vaccine or combined A+B vaccine [62, 63, 100, 101, 101A].**

<b>Vaccination Schedule</b>	<b>Advantages</b>	<b>Disadvantages</b>
0,7,21 days, 12 months	- Rapid immunity, - Short duration, - High antibody titres at 12 and 13 months - Potential for better uptake	- Not tested in HIV or other immunocompromised patients - Little published data - Low antibody titres in the first year ( but current evidence suggests that protection is still adequate in the immuno-competent)
0,1,2,12 months	- Early immunity, - Shorter time to early immunity than the 0,1,6 course - High antibody titres at 12 and 13 months	- Antibody titres lower than the 0,1,6 regimen in the first year
0,1,6 months	- Higher antibody titres at 7 months than the other two regimens although this may not be clinically important - Long established regimen	- Most researched in HIV - Poor uptake of the 6 month dose in the clinical setting

- It is probable that booster doses of vaccine are not required for at least fifteen years in immunocompetent children and adults who have responded to an initial vaccine course (III,B) [114-117]. HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when anti-HBs levels fall below 100i.u./l (III,B) [106, 114].

- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given four or more years later without the need to restart a three dose course (III,B) [118]. One or two doses of doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively [118, 119].

#### Hepatitis D (Delta virus infection, HDV)

This is an incomplete RNA virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of intravenous drug users (IVDUs) and their sexual partners but also in female sexworkers, and sporadically in other groups [120]. Suspect HDV in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive [24, 26, 54, 69]. There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis [24, 26, 54]. Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test [34, 69]. Response to anti-viral therapy is poor [121, 122].

### Hepatitis C virus (HCV) infection

#### Aetiology

An RNA virus in the flaviviridae family. It is endemic world-wide with high prevalence rates in South and East Asia and Eastern Europe [123]. UK prevalence rates vary from 0.06% in blood donors to over 60% in IVDUs [124]. 5572 cases were reported in England and Wales in 1999 [1].

#### Transmission

- Parenteral spread accounts for the majority of cases through shared needles/syringes in IVDUs, transfusion of blood or blood products (pre-1990s), renal dialysis, needle-stick injury or sharing a razor with an infected individual [125-130].
- Sexual transmission occurs at a low rate (approximately 0.2 – 2% per year of relationship, or 2-11% of spouses in long-term relationships) but these rates increase if the index patient is also HIV infected [131-138]. There is an increased rate of carriage (2%) in gay men attending GU clinics but this is largely linked to HIV co-infection [132, 133]. There is also evidence of increased rates of infection in female sex workers [61, 139], former prisoners, tattoo recipients and alcoholics [140-142].
- Vertical (mother to infant) spread also occurs at a low rate (5% or less in most studies), but higher rates (up to 40%) are seen if the woman is both HIV and HCV positive [127, 131, 143-145]. Increased rates of transmission are seen in Japanese patients and in all groups transmission risk correlates with the presence of detectable HCV-RNA in the mother's blood [144, 146, 147].
- Amongst blood donors, 50% of those with HCV infection do not admit to having risk factors [125, 148].

#### Clinical Features

##### Incubation period

Four to 20 weeks for the uncommon cases of acute hepatitis. HCV serology is usually positive (90%) three months after exposure but can take as long as nine months. Occasional cases of infection proven by RT-PCR (see "diagnosis") do not result in positive antibody tests [126, 127, 149-151].

##### Symptoms [126, 127]

- The majority of patients (>80%) undergo asymptomatic acute infection.
- The uncommon cases of acute icteric hepatitis are similar to hepatitis A.

##### Signs

- Acute icteric hepatitis - see hepatitis A.
- Chronic hepatitis - see hepatitis B

##### Complications

- Acute fulminant hepatitis is rare (<1% of all hepatitis C infections), but is particularly common after hepatitis A super-infection of chronic hepatitis C carriers [28, 126, 127].
- Approximately 50-85% of infected patients become chronic carriers - a state which is normally asymptomatic but may cause non-specific ill health [152-155]. Once established, the chronic carrier state rarely resolves spontaneously (0.02%/year) [152]. Symptoms/signs are worse if there is a high alcohol intake or other liver disease [156-159]. Significant liver disease can be present in the 35% of carriers who have normal serum aminotransferase levels, [126, 127, 160, 161].
- Mortality in acute hepatitis is very low (<1%) but 20-30% of chronic carriers will progress to severe liver disease after 14-20 years infection, with an increased risk of liver cancer (approximately 1-4% of all patients and up to 33% of those with cirrhosis) [126, 127, 172, 68,69,81, 158, 163-165]. HIV co-infection worsens the prognosis [135,166-168].
- Pregnancy- Acute icteric hepatitis as for hepatitis A [21]. For risk of vertical transmission see "transmission".

## Diagnosis

### Serology

- A screening antibody tests (usually an Enzyme-linked immuno-assay, ELISA) is initially performed and if positive a second test, such as a recombinant immuno-blot assay (RIBA), is used to confirm infection [23,78,79]. Third generation ELISA tests (ELISA-3) have an equivalent sensitivity to the RIBA assay [169]. Patients who are antibody positive on two occasions, six months apart, can be assumed to have chronic infection. Molecular biological techniques such as an RT-PCR assay for viral RNA are also available to confirm infection although 85-95% of RIBA/ELISA-3 positive patients will be RT-PCR positive [149-151, 169]. The RT-PCR does not reliably detect all HCV genotypes and is subject to inter-laboratory variability [149-151]. Recent guidelines from the British Society of Gastroenterology suggest using RT-PCR as a confirmatory assay following an ELISA-3 positive test ([www.bsg.org.uk/guidelines/clinguidehepc.pdf](http://www.bsg.org.uk/guidelines/clinguidehepc.pdf)) although this strategy is not currently widely used due to cost and lack of evidence of cost-effectiveness. All patients being considered for therapy should have a viral RNA test to confirm viraemia (see below).

### Other tests

- Acute infection - as for hepatitis A.
- Chronic infection - as for hepatitis B.

## Management

### General Advice

- Patients should be told not to donate blood, semen or organs and given advice on other routes of transmission (see below) (III, B) [123].
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Acute hepatitis C infection is a notifiable disease.

### Further Investigations

As for hepatitis B.

### Treatment

- Acute icteric hepatitis: There is some evidence that high dose alpha and/or beta interferon given during the acute phase will reduce the rate of chronicity to only 10% or less (IIb, B) [170-172]. Otherwise manage as for hepatitis A.
- Chronic infection: Alpha interferon 3-10 MU i.m. thrice weekly given for 3-12 months will abolish chronic infection in approximately 20-30% of patients (Ia, A) [173-178]. The addition of ribavirin (1000-1200 mg/day) will increase the response rate to 35-50% (Ia, A) [174, 179-181]. Patients are more likely to respond if they have less severe liver disease (low fibrosis index on liver biopsy), low serum HCV-RNA levels (<2million RNA copies/ml), if they are infected with certain HCV sub-types (types 2 and 3) or if they become HCV-RNA negative in the serum within four

weeks (Ib, A) [173, 180-187]. HIV-positive patients may respond to treatment (IIa, B) [188, 189]. Consensus interferon 9-15µg thrice weekly and pegylated interferon 180µg weekly also show promise (Ib, A) [190, 191], as does the addition of ketoprofen (Ib, A) or amantadine (IIa, B) to the other agents [192, 193]. For more information on therapy see the recent guidelines from the British Society of Gastroenterology ([www.bsg.org.uk/guidelines/clinguidehepc.pdf](http://www.bsg.org.uk/guidelines/clinguidehepc.pdf)).

- It is unclear whether chronically infected patients with a normal LFT (tested on two occasions) should be treated. If they have liver damage demonstrated on biopsy, they will respond to therapy, but less well than patients with abnormal LFT (Ib, A) [160, 194].
- Given the high rate of fulminant hepatitis in co-infection hepatitis A & C and the worse prognosis of hepatitis B & C co-infection, patients with hepatitis C should be vaccinated against hepatitis A and B (III,B) [28, 138, 139].

#### Pregnancy and Breast feeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see transmission) (IV, C) [131].
- Breast feeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load (III,B)[143, 144, 195].

#### Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (IV,C)[37]. The infectious period is from two weeks before the onset of jaundice in acute infection. If there was no acute infection trace back to the likely time of infection (e.g. blood transfusion, first needle sharing) although this may be impractical for periods longer than two or three years. Consider testing children born to infectious women (IV,C)[131]. For other non-sexual contacts thought to be at risk, discuss with the CCDC or equivalent.
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rate of transmission outside of HIV co-infection (see above), monogamous partners may choose not to use them (IV,C).

#### Follow-up

- As for hepatitis B (IV, C).
- Immunity is probably sub-type specific only - there are at least seven sub-types [149-151].

#### Screening and Primary Prevention.

- Consider testing for hepatitis C in all IVDUs, especially if equipment has been shared, in haemophiliacs or other patients who received blood or blood products pre-1990 and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown (III, B) [123, 125, 128-130, 133, 196]. Other groups to be considered for testing are sexual partners of HCV positive individuals, gay men, especially if HIV infected, female sex workers, tattoo recipients, alcoholics and ex-prisoners (III, B)[61, 123, 132, 133, 136-141]. It may take three months or more for the anti-HCV test to become positive after exposure (see “incubation period”).
- Since 1990 all donated blood in the UK has been screened for HCV and all blood products rendered incapable of transmitting infection (III, B) [197].
- Needle and syringe exchange schemes have led to a fall in parenterally transmitted infections including HCV, HBV and HIV, although not consistently (III, B) [198-200].

#### Auditable Outcomes

Acute hepatitis (A, B or C)

- Patients with acute hepatitis infection should be assessed clinically for severity, and have blood samples taken for serology, liver function, prothrombin time and renal function, all taken on the initial visit (target >90%)
- A clear treatment and follow-up plan should be stated in the notes (target 100%).

#### Hepatitis A

- If the clinic policy is to test and vaccinate gay men, - test for immunity (target >90%)
- - offer vaccination (target >90%)
- Provide written information on transmission and outcome of hepatitis A to infected patients (target >95%)

#### Hepatitis B

- Test patients in known at-risk groups for infection/immunity (target >90%)
- Offer vaccination to all non-immune patients at continuing risk (target >90%)
- In those offered vaccination, give a full course and test for post-vaccination response (target >50%)
- Provide written information on transmission and outcome of hepatitis B to infected patients (target >95%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of HBV-infected patients (target >95%)

#### Hepatitis C

- Ascertain the Hepatitis C and B status of intravenous drug users (target >80%)
- Provide written information on transmission and outcome of hepatitis C to infected patients (target >95%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of HCV-infected patients (target >95%)

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#### Conflict of Interest

None

#### Evidence Base

##### Medline

For each type of hepatitis, a medline search was performed for the years 1966 - 2000 (June) for hepatitis types A and B and 1990-2000 (June) for hepatitis C. From the MeSH terms "hepatitis A", "hepatitis B", and "hepatitis C", the following sub-headings were used: Complications, Drug Therapy, Diagnosis, Epidemiology, Etiology, Mortality, Prevention and Control, Therapy, Transmission, Virology. The searches were limited to "human" for all searches. For Drug Therapy, Prevention & Control, and Therapy searches were limited initially to "randomized controlled trials" but in the absence of enough publications this was changed to "controlled clinical trials", "clinical trials" or "reviews" in that order. For the sub-headings other than these three the search was limited to "reviews". Textword searches for "hepatitis A", hepatitis B", and "hepatitis C" were combined, as appropriate, with textword searches for "complication", "diagnosis", "prevention", "transmission", "immunoglobulin", "vaccine", "non-response", "non-responders", "HIV", "randomized controlled trial", "lamivudine", "famciclovir", "ribavirin"

##### Cochrane Library

The Cochrane library 2000 v2 (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Clinical Trial Register) was searched for all relevant articles using the textword "hepatitis".

### References

- [1] Anon. Viral hepatitis, England and Wales: laboratory reports. CDR weekly. 2000;10:24
- [2] Maguire HC, Handford S, Perry KR et al. A collaborative case-control study of sporadic hepatitis A in England. CDR Review 1995;5:R33-40
- [3] Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. J Hepatol 1993;18(suppl 2):S11-4
- [4] Minuk GY, Ding LX, Hannon C et al. The risks of transmission of acute hepatitis A and B virus infection in an urban centre. J Hepatol 1994;21:118-21
- [5] Melnick JL. History and epidemiology of hepatitis A virus. J Infect Dis 1995;171(suppl 1):S2-8
- [6] Hutin YJ, Pool V, Cramer EH et al. A multistate, foodborne outbreak of hepatitis A. N Engl J Med 1999;340:595-602
- [7] Massoudi MS, Bell BP, Paredes V, Insko J, Evans K, Shapiro CN. An outbreak of hepatitis A associated with an infected foodhandler. Pub Health Rep 1999;114:157-64
- [8] Stewart T, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. Med J Aust 1993;158:519-21
- [9] Leentvaar-Kuijpers A, Kool JL, Veugelers VJ et al. An outbreak of hepatitis A among homosexual men in Amsterdam. Int J Epidem 1995;24:218-22
- [10] Anon. Increased incidence of hepatitis A in south east England. CDR weekly 1997;7:373 & 376
- [11] Walsh B, Sundkvist T, Maguire H et al. Rise in hepatitis A among gay men in the Thames region 1995 and 1996. Genitourin Med 1996;72:449-50
- [12] Villano SA, Nelson KE, Vlahov D et al. Hepatitis A among homosexual men and injecting drug users: more evidence for vaccination. Clin Infect Dis 1997;25:726-8
- [13] Reintjes R, Bosman A, de Zwart O et al. Outbreak of hepatitis A in Rotterdam associated with visits to 'darkrooms' in gay bars. Comm Dis Pub Health 1999;2:43-6
- [14] Ferson MJ, Young LC, Stokes ML. Changing epidemiology of hepatitis A in the 1990s in Sydney, Australia. Epidemiol Infect 1998;121:631-6
- [15] Nandwani R, Caswell S, Boag F et al. Hepatitis A seroprevalence in homosexual and heterosexual men. Genitourin Med 1994;70:325-8
- [16] Corona R, Stroffolini T, Giglio A et al. Lack of evidence for increased risk of hepatitis A infection in homosexual men. Epidemiol Infect 1999;123:89-93
- [17] Grinde B, Stene-Johansen K, Sharma B et al. Characterisation of an epidemic of hepatitis A virus involving intravenous drug abusers - infection by needle sharing? J Med Virol 1997;53:69-75
- [18] Shaw DD, Whiteman DC, Merritt AD et al. Hepatitis A outbreaks among illicit drug users and their contacts in Queensland, 1997. MedJ Aust 1999;170:584-7
- [19] Stene-Johansen K, Skaug K, Blystad H, Grinde B. A unique hepatitis A virus strain caused an epidemic in Norway associated with intravenous drug abuse. Scand J Infect Dis 1998;30:35-8
- [20] Gil A, Gonzalez A, Dal-Re R et al. Prevalence of hepatitis A in an institution for the mentally retarded in an intermediate endemicity area: influence of age length of institutionalisation. 1999;38:120-3
- [21] Chudy M, Budek I, Keller-Stanislawski B et al. A new cluster of hepatitis A infection in hemophiliacs traced to a contaminated plasma pool. J Med Virol 1999;57:91-9
- [22] Soucie JM, Robertson BH, Bell BP, McCaustland KA, Evatt BL. Hepatitis A virus infections associated with clotting factor concentrate in the United States. Transfusion 1998;38:573-9
- [23] Polish LB, Robertson BH, Khanna B et al. Excretion of hepatitis A virus (HAV) in adults: comparison of immunologic and molecular detection methods and relationship between HAV positivity and infectivity in tamarins. J Clin Microbiol 1999;37:3615-17
- [24] McIntyre N. Clinical presentation of acute viral hepatitis. Brit Med Bull 1990;46:533-47
- [25] Sciot R, Van Damme B, Desmet VJ. Cholestatic features in hepatitis A. J Hepatol 1986;3:172-81
- [26] Fagan EA, Williams R. Fulminant viral hepatitis. Brit Med Bull 1990;46:462-80
- [27] Willner IR, Uhl MD, Howard SC et al. Serious hepatitis A: an analysis of patients hospitalised during an urban epidemic in the United States. Ann Int Med 1998;128:111-4
- [28] Vento S, Garfano T, Renzini C et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286-90

- [29] Inoue K, Yoshida M, Yotsuyanagi H et al. Chronic hepatitis A with persistent viral replication. *J Med Virol* 1996;50:322-4
- [30] Hieber JP, Dalton D, Shorey J, Combes B. Hepatitis and pregnancy. *J Pediatr* 1977;91:545-9
- [31] Medhat A, el-Sharkawy MM, Shaaban MM et al. Acute viral hepatitis in pregnancy. *Int J Gyn Obs* 1993;40:25-31
- [32] Leikin E, Lysikiewicz A, Garry D et al. Intrauterine transmission of hepatitis A virus. *Obstet Gynecol* 1996;88:690-1
- [33] Erkan T, Kutlu T, Cullu F, Tumay GT. A case of vertical transmission of hepatitis A infection. *Acta Paediatrica* 1998;87:1008-9
- [34] McPherson RA. Laboratory diagnosis of human hepatitis viruses. *J Clin Lab Anal.* 1994;8:369-77
- [35] Liaw YF, Yang CY, Chu CM et al. Appearance and persistence of hepatitis A IgM antibody in acute clinical hepatitis A observed in an outbreak. *Infection* 1986;14:156-8
- [36] Stapleton JT. Host immune response to hepatitis A virus. *J Infect Dis* 1995;171(suppl 1):S9-14
- \*[37] Oxman AD, Scott EA, Sellors JW et al. Partner notification for sexually transmitted diseases: an overview of the evidence. *Canadian J Pub Health* 1994;85(suppl 1):S41-7
- [38] Salisbury TM, Begg NT eds. Hepatitis A. In: *Immunisation against infectious disease*. London, HMSO. 1996:85-94
- [39] Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clin Infect Dis* 1992;14:580-6
- [40] Irwin DJ, Millership S. Control of a community hepatitis A outbreak using hepatitis A vaccine. *Comm Dis Pub Health* 1999;2:184-7
- [41] Mele A. efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomized trial. *Lancet* 1999;353:1136-9
- [42] Dagan R, Greenberg D, Goldenbetg-Gehtman B et al. Safety and immunogenicity of a new formulation of an inactivated hepatitis A vaccine. *Vaccine* 1999;17:1919-25
- [43] Lu MY, Chang MH, Tsai KS, Chen DS. Hepatitis A vaccine in healthy adults: a comparison of immunogenicity and reactogenicity between two- and three-dose regimens. *Vaccine* 1999;17:26-30
- [44] Vidor E, Ratheau C, Briantais P, Vuillier D. comparison of two immunisation schedules with an inactivated hepatitis A vaccine (Avaxim TM). *J Travel Med* 1998;5:167-72
- [45] Chan CY, Lee SD, Yu MI, et al. Long-term follow-up of hepatitis A vaccination in children. *Vaccine* 1999;17:369-72
- [46] Hess G, Clemens R, Bienzle U et al. Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. *J Med Virol* 1995;46:40-2
- [47] Neilsen GA, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and uninfected homosexual men. *J Infect Dis.* 1997;176:1064-7
- [48] Thompson SC, Norris M. Immunogenicity and reactogenicity of a combined hepatitis A-hepatitis B vaccine in adolescents. *Int J Infect Dis* 1998;2:193-6
- [49] Frey S, Dagan R, Ashur Y et al. Interference of antibody production to hepatitis B surface antigen in a combination hepatitis A/hepatitis B vaccine. *J Infect Dis* 1999;180:2018-22
- [50] Corona R, Stroffolini T, Giglio A et al. Lack of evidence for increased risk of hepatitis A infection in homosexual men. *Epidemiol Infect* 1999;123:89-93
- [51] Gay NJ, Hesketh LM, Osborne KP et al. The prevalence of hepatitis B infection in adults in England and Wales. *Epidemiol Infect* 1999;122:133-8
- [52] Hart GJ, Dawson J, Fitzpatrick RM et al. Risk behaviour, anti-HIV and anti-hepatitis B core prevalence in clinic and non-clinic samples of gay men in England, 1991-1992. *AIDS* 1993;7:863-9
- [53] Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. *Lancet* 1989;i:889-93
- [54] Hoofnagle JH. Chronic hepatitis B. *N Engl J Med* 1990;323:337-9
- [55] Osella AR, Massa MA, Joeke S et al. Hepatitis B and C virus sexual transmission among homosexual men. *Am J Gastroenterol* 1998;93:49-52
- [56] Gilson RJ, de Ruiter A, Waite J et al. Hepatitis B virus infection in patients attending a genitourinary medicine clinic: risk factors and vaccination coverage. *Sex Trans Inf* 1998;74:110-5
- [57] Struve J, Giesecke J, Lindh G et al. Heterosexual contact as a major route for transmission of acute hepatitis B amongst adults. *J Infect.* 1990;20:111-21
- [58]. Balogun MA, Ramsay ME, Fairley CK, Collins M, Heptonstall J. Acute hepatitis B infection in England and Wales: 1985-96. *Epidemiol Infect* 1999;122:125-31

- [59] Huo TI, Wu JC, Huang YH et al. Evidence of transmission of hepatitis B to spouses from sequence analysis of the viral genome. *J Gastroenterol Hepatol* 1998;13:1138-42
- [60] Hyams KC, Phillips IA, Tejada A, Hepatitis B in a highly active prostitute population: evidence for a low risk of antigenaemia. *J Infect Dis* 1990;162:295-8
- [61] Ward H, Day S, Weber J. Risky business: health and safety in the sex industry over a 9 year period. *Sex Trans Infect* 1999;75:340-3
- [62] Salisbury TM, Begg N eds. Hepatitis B. In: *Immunisation against infectious disease*. London, HMSO. 1996;95-108
- [63] Palmovich D, Crnjakovic-Palmovic J et al. Prevention of hepatitis B virus (HBV) infection in health-care workers after accidental exposure: a comparison of two prophylactic schedules. *Infection* 1993;21:42-5
- [64] Brook MG., Lever AML., Griffiths P., et al. Antenatal screening for hepatitis B is medically and economically effective in the prevention of vertical transmission: Three years experience in a London hospital. *Quart.J.Med.* 1989; 264:313-317.
- [65] Walsh B, Maguire H, Carrington D. Outbreak of hepatitis B in a acupuncture clinic. *Comm Dis Pub Health* 1999;2:137-40
- [66] Cramp ME, Grundy HC, Perinpanayagam RM et al. Seroprevalence of hepatitis B and C virus in two institutions caring for mentally handicapped adults. *J Roy Soc Med* 1996;89:401-2
- [67] Kiire CF. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and sub-tropical Africa. *Gut* 1996;38(suppl 2):S5-12
- [68] Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995;20:992-1000
- [69] Gitlin N. Hepatitis B: diagnosis, prevention and treatment. *Clin Chem* 1997;43:1500-6
- [70] Brook MG., Chan G., Yap I et al. Randomised controlled trial of lymphoblastoid interferon alfa in European men with chronic hepatitis B virus infection. *Br.Med.J.* 1989; 299:652-656.
- [71] Brook MG., McDonald JA., Karayiannis P., Caruso L., Forster G., Thomas HC. Randomised controlled trial of interferon alfa 2a (rbe) (Roferon A) for the treatment of chronic hepatitis B virus (HBV) infection: factors that influence response. *Gut* 1989; 30:1116-1122.
- [72] Brook MG., Karayiannis P., Thomas HC. Which patients with chronic hepatitis B will respond to alpha interferon therapy? A statistical analysis of predictive factors. *Hepatology* 1989; 10:761-763.
- [73] Nevens F, Main J, Honkoop P et al. Lamivudine therapy for chronic hepatitis B: a six-month randomized dose-ranging study. *Gastroenterol* 1997;113:1258-63
- [74] Steinberg JL, Yeo W, Zhong S et al. Hepatitis B reactivation in patients undergoing cytotoxic chemotherapy for solid tumours: precore/core mutations may play an important role. *J Med Virol* 2000;60:249-55
- [75] Chu CM, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. *Gut* 1999;45:613-7
- [75] Zarski JP, Bohn B, Bastie A et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998;28:27-33
- [77] Chiaramonte M, Stroffolini T, Vian A et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132-7
- [78] Colin JF, Cazals -Hattem D, Lorient MA et al. Influence of immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29:1306-10
- [79] el-Dalil A, Radcliffe KW, Bailey J et al. A survey on hepatitis B vaccination policies in genitourinary medicine in the UK and Ireland. *Genitourin Med* 1995;71:251-3
- [80] Janssen HL, Gerken G, Carreno V et al. Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1999;30:238-43
- [81] Carreno V, Marcellin P, Hadziyannis S et al. Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alfa-2a. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1999;30:277-82
- [82] Lai CL, Ching CK, Tung AK et al. Lamivudine is effective in suppressing hepatitis B virus DNA in Chinese hepatitis B surface antigen carriers: a placebo-controlled trial. *Hepatology* 1997;25:241-4
- [83] Main J, Brown JL, Howells C et al. A double-blind, placebo-controlled study to assess the effect of famciclovir on virus replication in patients with chronic hepatitis B virus infection. *J Vir Hepatitis* 1996;3:211-5
- [84] Dienstag JL, Schiff ER, Wright TL et al. Lamivudine as initial treatment of chronic hepatitis B in the United States. *New Engl J Med* 1999;341:1256-63

- [85] Marques AR, Lau DT, McKenzie R, Straus SE, Hoofnagle JH. Combination therapy with famciclovir and interferon-alpha for the treatment of chronic hepatitis B. *J Infect Dis*. 1998;178:1483-7
- [86]. Tsiang M, Rooney JF, Toole JJ, Gibbs CS. Biphasic clearance kinetics of hepatitis B virus from patients during adefovir dipivoxil therapy. *Hepatology* 1999;29:1863-9
- [87] Cotonat T, Quiroga JA, Lopez-Alcorocho JM et al. Pilot study of combination therapy with ribavirin and interferon alfa for the retreatment of chronic hepatitis B e antibody-positive patients. *Hepatology* 2000;31:502-6
- [88] Chien RN, Liaw YF, Chen TC, Yeh CT, Sheen IS. Efficacy of thymosin alpha1 in patients with chronic hepatitis B: a randomized, controlled trial. *Hepatology* 1998; 27:1383-7
- [89] Ikeda K, Saitoh S, Suzuki Y et al. Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study. *Cancer* 1998;82:827-35
- [90] Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999;29:971-5
- [91] Thibault V, Benhamou Y, Seguret C et al. Hepatitis B virus (HBV) mutations associated with resistance to lamivudine in patients coinfecting with HBV and human immunodeficiency virus. *J Clin Microbiol* 1999;37:3013-6
- [92] Dore GJ, Cooper DA, Barrett C et al. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfecting persons in a randomized controlled study (CAESAR). The CAESAR Coordinating Committee. *J Infect Dis* 1999;180:607-13
- [93] Rayes N, Seehofer D, Bechstein WO et al. Long-term results of famciclovir for recurrent or de novo hepatitis B virus infection after liver transplantation. *Clin Transplant* 1999;13:447-52
- [94] Xiong X, Yang Y, Westland CE, Zou R, Gibbs Cs. In vitro evaluation of hepatitis B polymerase mutations associated with famciclovir resistance. *Hepatology* 2000; 31:219-24
- \*[95] Andre FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. *J Med Virol* 1994;44:144-51
- [96] Michielsen PP, Van Damme P. Viral hepatitis and pregnancy. *Acta Gastroenterologica Belgica* 1999;62:21-9
- [97] Gilson RJC, Anderson J, Brink N et al. Hepatitis B screening and immunisation in Genitourinary Medicine clinics. North Thames Regional Audit. Nov 1994
- [98] Sutherland S, Tilzey A. Guidelines for hepatitis B screening and vaccination. South Thames (East) Genitourinary Medicine Audit Group. 29<sup>th</sup> January 1993.
- [99] Anon. Specific immunoglobulin in the prevention of hepatitis B. *Lancet* 1975;ii:1132-4
- \*[100] Systematic Review: Jefferson T, Demicheli V, Deeks J et al. Vaccines against hepatitis B in health-care workers. *Cochrane Library*: Last amended 30 April 1997
- [101] Francis DP, Hadler SC, Thompson SE et al. The prevention of hepatitis B with vaccine. Report of the Centers for disease Control multi-center trial among homosexual men. *Ann Int Med* 1982;97:362-6
- [101A] Nothdurft, HD, Dietrich M, Zuckereman JN et al. A new accelerated vaccination schedule for rapid protection against hepatitis A and B. *Vaccine* 2002;20:1157-62
- [102] Allain JP, Hewitt PE, Tedder RS, Williamson LM. Evidence that anti-HBc but not HBV DNA testing may prevent some HBV transmission by transfusion. *Br J Haematol* 1999;107:186-95
- [103] Gutierrez C, Leon G, Loureiro CL et al. Hepatitis B virus DNA in blood samples positive for antibodies to core antigen and negative for surface antigen. *Clin Daig Lab Immunol* 1999;6:768-70
- [104] Wong KL, Bodsworth NJ, Slade MA et al. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. *Int J STD AIDS* 1996;7:490-4
- [105] Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. *AIDS* 1994;8:558-9
- [106] Rey D, Krantz V, Partisani M et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects in HIV-1 viral load. *Vaccine* 2000;18:1161-5
- [107] Clemens R, Sanger R, Kruppenbacher J et al. Booster immunisation of low- and non-responders after a standard three dose hepatitis B vaccine schedule- results of post-marketing surveillance. *Vaccine* 1997;15:349-52
- [108]. Goldwater PN. Randomized, comparative trial of 20 micrograms vs 40 micrograms Engerix B vaccine in hepatitis B vaccine non-responders. *Vaccine* 1997;15:353-6

- [109] Haubitz M, Ehlerding G, Beigel A et al. Clinical experience with a new recombinant hepatitis B vaccine in previous non-responders with chronic renal insufficiency. *Clin Nephrol* 1996; 45:180-2
- [110] Zuckerman JN, Sabin C, Craig FM et al. Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine: randomised double-blind dose-response study. *Br Med J* 1997;314:329-33
- [111] Heineman TC, Clements-Mann ML, Poland GA et al. A randomized controlled study in adults of the immunogenicity of a novel hepatitis B vaccine containing MF59 adjuvant. *Vaccine* 1999;17:2769-78
- [112] Zuckerman JN. Hepatitis B third generation vaccines: improved response and conventional vaccine non-response – third generation pre-S/S vaccines overcome non-response. *J Viral Hep* 1998;5(suppl 2):13-5
- [113] Eyigun CP, Yilmaz S, Gul C et al. A comparative trial of two surface subunit recombinant hepatitis B vaccines vs a surface and pre-S subunit vaccine for immunization of healthy adults. *J Viral Hep* 1998;5:265-9
- [114] European consensus group on hepatitis B immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000;355:561-65
- [115] Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? *J Infect Dis* 1999;179:489-92
- [116] Yuen MF, Lim WL., Cheng CC, Lam SK, Lai CL. Twelve year follow-up of a prospective randomized trial of recombinant DNA yeast vaccine versus plasma-derived vaccine without booster doses in children. *Hepatology* 1999;29:924-7
- [117] Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, McMahon BJ. Protection provided by hepatitis B vaccine in a Yupik Eskimo population: results of a 10-year study. *J Infect Dis* 1997;175:674-7
- [118] Wistrom J, Ahlm C, Lundberg S, Settergren B, Tarnvik A. Booster vaccination with recombinant hepatitis B vaccine four years after priming with one single dose. *Vaccine* 1999;17:2162-5
- [119] Marsano LS, West DJ, Chan I et al. A two dose hepatitis B vaccine regimen: proof of priming and memory responses in young adults, *Vaccine* 1998;16:624-9
- [120] Mele A, Franco E, Caprilli F et al. Hepatitis B and delta virus infection among heterosexuals, homosexuals and bisexual men. *Eur J Epidemiol*. 1988;4:488-9
- [121] Puoti M, Rossi S, Forleo MA et al. Treatment of chronic hepatitis D with interferon alfa-2b in patients with human immunodeficiency virus infection. *J Hepatol* 1998;29:45-52
- [122] Lau DT, Doo E, Park Y et al. Lamivudine for chronic delta hepatitis. *Hepatology* 1999;30:546-9
- [123] Alter M. Epidemiology of hepatitis C. *Hepatology* 1997;26 (suppl 1):62S-65S
- [124] Lamden KH, Kennedy N, Beeching NJ et al. Hepatitis B and hepatitis C virus infections: risk factors among drug users in Northwest England. *J Infect* 1998;37:260-9
- [125] Kaldor JM, Archer GT, Buring ML et al. Risk factors for hepatitis C virus infection in blood donors: a case-control study. *Med J Aust* 1992;157:227-30
- [126] Hoofnagle J. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;26(suppl 1):15S-20S
- [127] Seeff LB. Natural history of hepatitis C. *Hepatology* 1997;26(suppl 1):21S-28S
- [128] Ramsay ME, Balogun MA, Collins M, Balraj V. Laboratory surveillance of hepatitis C virus infection in England and Wales: 1992-1996. *Comm Dis & Pub Health* 1998;1:89-94
- [129] Hamid SS, Farooqui B, rizvi Q, Sultana T, Siddiqui AA. Risk of transmission and features of hepatitis C after needlestick injuries. *Infect Control & Hosp Epidemiol* 1999;20:63-4
- [130] Sawayama Y, Hayashi J, Kakuda K et al. Hepatitis C virus infection in institutionalized psychiatric patients: possible role of transmission by razor sharing. *Digest Dis Sci* 2000;45:351-6
- [131] Dienstag JL. Sexual and perinatal transmission of hepatitis C. *Hepatology* 1997;26(suppl 1):66S-70S
- [132] Tedder RS, Gilson RJC, Briggs M et al. Hepatitis C virus: evidence for sexual transmission. *Brit Med J* 1991;302:1299-1302
- [133] Bodsworth NJ, Cunningham P, Kaldor J et al. Hepatitis C virus infection in a large cohort of homosexually active men: independent associations with HIV-1 infection and injecting drug use but not sexual behaviour. *Genitourin Med* 1996;72:118-22
- [134] Akahane Y, Kojima M, Sugai Y et al. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. *Ann Intern Med* 1994;120:748-52

- [135] Zylberberg H, Pol S. Reciprocal interactions between human immunodeficiency virus and hepatitis C virus infections. *Clin Infect Dis* 1996;23:1117-25
- [136] Neumayr G, Propst A, Schwaighofer H, Judmaier G, Vogel W. Lack of evidence for the heterosexual transmission of hepatitis C. *QJM* 1999;92:505-8
- [137] Guadagnino V, Stroffolini T, Foca A et al. Hepatitis C virus infection in a family setting. *Eur J Epidemiol* 1998;14:229-32
- [138] Satoglu N, Tasova Y, Butgut R, Dundar IH. Sexual and non-sexual intrafamilial spread of hepatitis C virus: intrafamilial transmission of HCV. *Eur J Epidemiol* 1998;14:225-8
- [139] Mesquita PE, Granato CF, Castelo A. Risk factors associated with hepatitis C virus (HCV) infection among prostitutes and their clients in the city of Santos, Sao Paulo state, Brazil. *J Med Virol* 1997;51:338-43
- [140] Balasekaran R, Bulterys M, Jamal MM et al. A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States. *Am J Gastroenterol* 1999;94:1341-6
- [141] Delage G, Infante-Rivrd C, Chiavetta JA et al. Risk factors for acquisition of hepatitis C virus infection in blood donors: results of a case control study. *Gastroenterol* 1999;116:893-9
- [142] Murphy EL, Bryzman SM, Glynn SA et al. Risk factors for hepatitis C virus infection in United States blood donors. NHLBI Retrovirus Epidemiology Donor Study (REDS). *Hepatology* 2000;31:756-62
- [143] Kumar RM, Shahul S. Role of breast-feeding in transmission of hepatitis C virus to infants of HCV-infected mothers. *J Hepatol* 1998;29:191-7
- [144] Resti M, Azzari C, Mannelli F et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. *BMJ* 1998;317:437-41
- [145] Papaevangelou V, Pollack H, Rochford G et al. Increased transmission of vertical hepatitis C virus (HCV) infection to human immunodeficiency virus (HIV)-infected infants of HIV- and HCV-coinfected women. *J Infect Dis* 1998;178:1047-52
- [146] Xiong SK, Okajima Y, Ishikawa K et al. Vertical transmission of hepatitis C virus, risk factors and infantile prognosis. *J Obs Gyn Res* 1998;24:57-61
- [147] Giacchino R, Tasso L, Timitilli A et al. Vertical transmission of hepatitis C virus infection: usefulness of viraemia detection in HIV-seronegative hepatitis C virus-seropositive mothers. *J Ped* 1998;132:167-9
- [148] Atrah HI, Ala FA, Ahmed MM et al. Unexplained hepatitis C virus antibody seroconversion in established blood donors. *Transfusion* 1996;36:339-43
- [149] Dore GJ, Kaldor JM, McCaughan W. Systematic review of role of polymerase chain reaction in defining infectiousness in people infected with hepatitis C virus. *Brit Med J* 1997;315:333-7
- [150] Gretch DR. Diagnostic tests for hepatitis C. *Hepatology* 1997;(suppl 1):43S-47S
- [151] Lok ASF, Gunaratnam NT. Diagnosis of hepatitis C. *Hepatology* 1997;26(suppl 1):48S-56S
- [152] Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999;29:908-14
- [153] Bonkovsky HL, Wooley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. *Hepatology* 1999;29:264-7
- [154] Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C on quality of life. *Hepatology* 1999;30:1299-301
- [155] Barkhuizen A, Rosen HR, Wolf S et al. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. *Am J Gastroenterol* 1999;94:1355-60
- [156] Pol S, Lamorthe B, Thi NT et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. *J Hepatol* 1998;28:945-50
- [157] Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998;28:805-9
- [158] Chiaramonte M, Stroffolini T, Vian A et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132-7
- [159] Chu CM, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. *Gut* 1999;45:613-7
- [160] Van Thiel DH, Caraceni P, Molloy PJ et al. Chronic hepatitis C in patients with normal or near normal aminotransferase levels: the role of interferon alpha 2b therapy. *J Hepatol* 1995;23:503-8
- [161] Bellentani S, Pozzato G, Saccoccio G et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the dionysos study. *Gut* 1999;44:874-80

- [162] Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology* 1997;26(suppl 1):34S-38S
- [163] Seef LB. Natural history of hepatitis C. *Am J Med* 1999;107:10S-15S
- [164] Lopez –Morante A, Saez-Royuela F, Echevarria C et al. Influence of the transmission route and disease duration in the histopathology of chronic hepatitis C: a study of 101 patients. *Eur J Gastro Hepatol* 1998;10:15-9
- [165] Tarao K, Rino Y, Ohkawa S et al. Association between high serum alanine aminotransferase levels and more rapid development and higher rate of incidence of hepatocellular carcinoma in patients with hepatitis C virus-associated cirrhosis. *Cancer* 1999;86:589-95
- [166] Piroth L, Duong M, Quantin C et al. Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? *AIDS* 1998;12:381-8
- [167] Allory Y, Charlotte F, Benhamou Y et al. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: a case-control study. *Hum Pathol* 2000;31:69-74
- [168] Lesens O, Deschenes M, Steben M et al. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive haemophiliacs and should be treated as an opportunistic infection. *J Infect Dis* 1999;179:1254-8
- [169] Mohan KV, Murkavel KG, Rajaninkanth R et al. Diagnosis of hepatitis C virus infection by ELISA, RIBA and RT-PCR: a comparative evaluation. *Ind J Gastroenterol* 1999;18:73-5
- [170] Vogel W, Graziadei I, Datz C et al. High-dose interferon-alpha 2b treatment prevents chronicity in acute hepatitis C: a pilot study. *Dig Dis Sci* 1996;41(suppl 12):81S-85S
- [171] Oketani M, Higashi T, Yamasaki M et al. Complete response to twice-a-day interferon-beta with standard interferon-alpha therapy in acute hepatitis C after a needle-stick. *J Clin Gastroenterol* 1999;28:49-51
- [172] Takagi H, Uehara M, Kakizaki S et al. Accidental transmission of HCV and treatment with interferon. *J Gastroenterol Hepatol* 1998;13:238-43
- [173] Davis GL, Lau JYN. Factors predictive of a beneficial response to therapy of hepatitis C. *Hepatology* 1997;26(suppl 1):122S-127S
- [174] Schalm SW, Hansen BE, Chemello L et al. Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. Meta-analysis of individual patient data from European centres. *J Hepatol* 1997;26:961-6
- \*[175] Poynard T, Leroy V, Cohard M et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996;24:778-89
- \*[176] Niederau C, Heintges T, Haussinger D et al. Treatment of chronic hepatitis C with alpha-interferon: an analysis of the literature. *Hepato-Gastroenterol* 1996;43:1544-56
- [177] Nomura H, Tsuchiya Y, Maruyama T et al. The effects of a high dose, short course of interferon on hepatitis C. *J Gastro Hepatol* 1999;14:85-9
- [178] Ascione A, De Luca M, Canestrini C et al. Efficacy of high dose of recombinant alpha 2b interferon on long term response in chronic hepatitis C and cirrhosis: prospective randomized multicentre study. *Ital J Gastro Hepatol* 1998;30:517-23
- [179] Reichard O, Norkrans G, Fryden A et al. Randomized, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. *Lancet* 1998;351:83-7
- [180] McHutchison JG, Gordon SC, Schiff ER et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998;339:1485-92
- [181] Poynard T, Marcellin P, Lee SS et al. Randomized trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998;352:1426-32
- [182] Davis GL, Esteban-Mur R, Rustgi V et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N Engl J Med* 1998;339:1493-9
- [183] Martinot-Peignoux M, Boyer N, Pouteau M et al. Predictors of sustained response to alpha interferon therapy in chronic hepatitis C. *J Hepatol* 1998;29:214-23
- [184] Brouwer JT, Nevens F, Kleteer B et al. Efficacy of interferon dose and prediction of response in chronic hepatitis C. Benelux study in 336 patients. *J Hepatol* 1998;28:951-9
- [185] Bellobuono A, Mondazzi L, Tempini S et al. Should patients with early loss of HCV-RNA during alpha interferon therapy for chronic hepatitis C be treated for 6 or 12 months? *J Hepatol* 1999;30:8-13
- [186] Kagawa T, Hosoi K, Takashimuzi S et al. Comparison of two interferon alfa treatment regimens characterized by an early virological response in patients with chronic hepatitis C. *Am J Gastroenterol* 1998;93:192-6

- [187] Montalto G, soresi M, Carroccio A et al. Comparative responses to three different types of interferon-alpha in patients with chronic hepatitis C. *Curr Med Res Opinion* 1998;14:235-41
- [188] Soriano V, Gacia-Samaniego J, Bravo R et al. Efficacy and safety of alpha-interferon for chronic hepatitis C in HIV-infected patients. HIV-hepatitis Spanish study group. *J Infect* 1995;31:9-13
- [189] Expert perspectives panel. Strategies for the management of HIV/HCV coinfection. 20 pages. [www.projectsinknowledge.com/hiv-hcv/index.html](http://www.projectsinknowledge.com/hiv-hcv/index.html)
- [190] Jensen DM, Krawitt EL, Keefe EB et al. Biochemical and viral response to consensus interferon (CIFN) therapy in chronic hepatitis C patients: effect of baseline viral concentration. Consensus interferon study group. *Am J Gastroenterol* 1999;94:3583-8
- [191] Zeuzem S, Feinman SV, Rasenack J et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *New Engl J Med* 2000;343:1666-72
- [192] Munoz AE, Levi D, Podesta A et al. Interferon-alpha 2b combined with ketoprofen administration improves virological response in chronic hepatitis C: a prospective and randomised trial. *Gut* 2000;46:427-31
- [193] Brillanti S, Foli M, Di Tomaso M et al. Pilot study of triple antiviral therapy for chronic hepatitis C in interferon alpha non-responders. *Ital J Gastroenterol Hepatol* 1999;31:130-4
- [194] Sangiovanni A, Morales R, Spinzi G et al. Interferon alfa treatment of HCV-RNA carriers with persistently normal transaminase levels: a pilot randomized controlled study. *Hepatology* 1998;27:853-6
- [195] Polywka S, Schroter M, Feucht HH, Zollner B, Laufs R. Low risk of vertical transmission of hepatitis C virus by breast milk. *Clin Infect Dis* 1999;29:1327-9
- [196] Anon. Hepatitis C virus: guidance on the risks and current management of occupational exposure. PHLS hepatitis subcommittee. *CDR Review* 1993;3:R135-9
- [197] Regan FA, Hewitt P, Barbara JA, Contreras M. Prospective investigation of transfusion transmitted infection in recipients of over 20,000 units of blood. *BMJ* 2000;320:403-6
- [198] Hagan H, MCGough JP, Thiede H et al. Syringe exchange and risk of infection with hepatitis B and C viruses. *Am J Epidemiol* 1999;149:203-13
- [199] Goldberg D, Cameron S, McMenamin J. Hepatitis C virus antibody prevalence among injecting drug users in Glasgow has fallen but remains high. *Comm Dis Pub Health* 1998;1:95-7
- [200] van Beek I, Dwyer R, Dore GJ, Luo K, Kaldor JM. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *BMJ* 1998;317:433-7

\* These references are reviewed in the Cochrane Library.